REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 174, 180, 183, and 208 are amended. Claims 173-194, 196-203, 205-211, and 231 are now pending in this application.

The 35 U.S.C. § 112 Rejections

Claims 173-181, 183 and 208 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for "decreasing lipid accumulation" in claims 178 and 208 and "reducing diabetic retinopathy" in claim 183, allegedly does not reasonably provide enablement for "inhibiting" or "inhibits" lipid accumulation or diabetic retinopathy. It is Applicant's position that an agent of the invention that "decreases" lipid accumulation or "reduces" diabetic retinopathy, "inhibits" lipid accumulation and "inhibits" diabetic retinopathy, respectively. Nevertheless, to provide consistency, claims 174, 183 and 208 are amended.

Accordingly, withdrawal of the § 112(1) enablement rejection is respectfully requested.

Claim 231 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claim 231 was also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner asserts that the specification does not describe the specific requisite of a small vessel disease and that the term "small vessel disease" is indefinite. These rejections are respectfully traversed.

It is Applicant's position that the phrase "small vessel disease" is understood and conventionally used in the art (see enclosures from www.heartofnewlife.com; www.healthandage.com; and www.alzheimers.org.uk). Applicant need not teach what is well known to the art. Moreover, assuming for the sake of argument the phrase "small vessel disease" was not conventionally used in the art, the specification discloses that small vessel disease includes silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy and retinopathy. Thus, the phrase "small vessel disease" in the claims is clear.

Therefore, withdrawal of the § 112(1) written description rejection, and the § 112(2) rejections over the phrase "small vessel disease", is respectfully requested.

The 35 U.S.C. § 102 Rejection

Claims 173-174, 178-183, 186-191, 196-201, 205-208, 210-211, and 231 were rejected under 35 U.S.C. § 102(b) as being anticipated by Nuovo et al. (Int. J. Gyn. Path., 8:125 (1989)). This rejection is respectfully traversed.

Nuovo et al. report that tamoxifen treatment in postmenopausal women with metastatic breast cancer may be associated with endometrial polyp proliferation. In particular, it is disclosed that the endometrial polyps in these patients were large, indicating marked proliferation. Histology for the three case studies showed marked cystic glandular hyperplasia within a fibrotic stroma and large, thick walled blood vessels (pages 126 and 128).

Claims 173-174, 178-183, 186-191, 196-206, 205-208, 210-211, and 231 recite the use of agents other than tamoxifen, i.e., claim 173, and claims 174, 178-181, 196-199 and 205-206 as they depend on claim 173; claim 182, and claims 183, 186-191, 196-199, and 205-206 as they depend on claim 182; claim 207, and claims 208 and 210-211 as they depend on claim 207; and claim 231; exclude tamoxifen by proviso ("with the proviso that when R^4, R^5, and R^6 are H, R^3 is not ethyl").

Moreover, claim 200, and claims 201-203 and 205-206 as they depend on claim 200, are directed to the use of an agent having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.

Therefore, withdrawal of the § 102(b) rejection is respectfully requested.

The Nonstatutory Obviousness-Type Double Patenting Rejections

Claims 173-194, 196-203, 205-211, and 231 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending application Serial No. 10/729,056. Claims 173-194, 196-203, 205-211, and 231 were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587.

As Serial No. 10/729,056 has not issued, a terminal disclaimer is not required.

Claim 8 in the '587 patent is directed to a method for lowering serum cholesterol, where R^9 in the compound of formula (VI) can be a variety of groups but none of these include ethyl or chloroethyl. In contrast, R^3 in the compound of formula (I) in claims 173, 182, 207, and 231 is

ethyl or chloroethyl, and claim 200 is directed to a method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter, wherein the agent has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 175-177, 184-185, 192-194, 202-203, and 209 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nuovo et al. Claims 173-181, 205-211 and 231 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)). Claims 182-194, 196-203 and 205-206 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Warri (Dissertation Abstracts International, 1993). These rejections are respectfully traversed

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner acknowledges that Nuovo et al. do not teach the use of the specified tamoxifen analogs to treat a mammal suffering from diabetes or retinopathy (page 9 of the Office Action). However, the Examiner asserts it would have been obvious to one of ordinary skill in the art to employ tamoxifen analogs for the treatment of patients having endometrial polyps with thick-walled blood vessels in postmenopausal patients because Nuovo et al. teach that tamoxifen is useful for the treatment of patients afflicted or having risk of developing thick-walled blood

vessels and because homologs, isomers or close structural analogs of tamoxifen have a viable utility.

In fact, Nuovo et al. teach that tamoxifen treatment is associated with endometrial polyp proliferation and thick-walled blood vessels, which provides a teaching away of using tamoxifen and analogs thereof in cardiovascular or vascular indications characterized by a decreased lumen diameter. Further, Nuovo et al. do not suggest, or provide a motivation to use, the recited compounds.

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was administered to female rats (page 1 of the translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day, and that the administered dose was 5 ml/mg. These amounts were based on earlier studies where a 0.7 mg/ml group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada et al. at page 13. Sawada et al. is therefore teaching against the use of such dosages, due to the associated toxicity. In addition, Sawada et al. fail to teach, suggest, or imply that toremifene is or could be a therapeutic anti-cholesterol agent. Based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGFβ levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. In addition, an abnormal estrous cycle was observed in the 0.1 mg/kg group, and uterine atrophy and the absence of an estrous cycle occurred for nearly three weeks in the 1 mg/kg group (page 9 of the translation).

Accordingly, because of the toxic effects of toremifene, and because the cause of total cholesterol reduction is unclear, Sawada et al. do not provide the suggestion or motivation to reach the present invention, e.g., the use of a compound of formula (I) to prevent or treat a mammal having or at risk of a cardiovascular or vascular indication characterized by a decreased lumen diameter.

Applicant submits that there is insufficient suggestion or motivation to modify Warri to reach the present claims. Warri discloses that, in breast cancer cells, toremifene increases TGFβ1 and promotes apoptosis. See Warri at page 51 ("TGFβ1 mRNA levels were enhanced only after higher concentration of toremifene, and not after E2-withdrawal").

First, the conclusions of Warri are specific to breast cancer cells. Warri does not provide the suggestion or motivation for a person of ordinary skill in the art to extrapolate the results for breast cancer cells found in Warri to non-breast cancer cells, and even so, Warri teaches away from the use of toremifene in conditions where apoptosis is undesirable, e.g., in conditions other than cancer. Similarly, a person of ordinary skill in the art would not have a reasonable expectation of success in utilizing toremifene to treat cardiovascular indications, because there is no teaching that toremifene would have the same TGFβ1 increasing effect in cells other than breast cancer cells. Accordingly, because the conclusions of Warri are specific to breast cancer, a skilled artisan would not have sufficient suggestion or motivation to reach the present invention, and would not have a reasonable expectation of success of treating a cardiovascular or vascular indication with tamoxifen analogs such as toremifene.

Moreover, Applicant submits that Warri does not disclose the use of toremifene or other tamoxifen analogs to treat retinopathy or diabetes as recited in claims 183-185, nor does Warri disclose the administration of toremifene or other tamoxifen analogs to a mammal at risk of or afflicted with a cardiovascular or vascular indication ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination...A statement that modification of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all of the aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references") (emphasis in original). M.P.E.P. § 2143.01. Accordingly, because the Examiner has not provided an objective reason to modify Warri with regard to retinopathy and diabetes, Warri does not teach all of the limitations of the claims.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date February 6, 2007 By

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 6th day of February 2007.

Dawn M. Poole

Name

Signature